DESCRIPTION OF REQUIREMENT

a. Objectives and Desired Results

The overall objective of the LTRC is to enable better management of lung diseases by increasing understanding of the pathogenetic mechanisms of these diseases through molecular histopathological studies of human lung tissues with and without disease. Primary emphases will be on chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis; secondary objectives may address other pulmonary diseases. The LTRC will collect lung tissue specimens, with corresponding clinical data from donor subjects, and make available these collections to lung disease researchers. Priority will be given to the collection of specimens that can be divided or replicated for distribution to many investigators.

Specimens and clinical data appropriate to specific diseases will be collected from approximately 810-1620 donor subjects. It is anticipated that donor subjects will be enrolled at a rate of 3-6 per month at each of the Clinical Centers over a 54 month period.

b. Background Information

Chronic diseases of the lung are a major cause of death and disability among Americans. Some of these diseases are highly prevalent. For example, chronic obstructive pulmonary disease (COPD) affects over 15 million people in this country and is now the fourth leading cause of death. Other lung diseases are less common but are very severe. For example, idiopathic pulmonary fibrosis has a prevalence of approximately 28 cases per 100,000 and is associated with 50-70% mortality at 5 years after diagnosis. Chronic pulmonary diseases tend to be: 1) associated with an inflammatory process in the lungs; 2) progressive; 3) inadequately controlled by current therapies, and 4) poorly understood in terms of pathogenetic mechanisms. Research is needed that will foster the development of novel therapeutic approaches for these conditions.

Since recognition of pathways involved in pathogenesis can lead to the identification of causative agents and therapeutic targets, an important avenue of research regarding chronic lung diseases is characterization of cellular and molecular abnormalities that correlate with disease presence, severity, and outcome. Powerful tools of molecular histopathology are now available that allow studies of inflammatory cell types, gene expression, protein content, cellular phenotype, and microbial and viral infection with exquisite sensitivity and high spatial resolution. The commercial availability of antibodies for routine immunohistochemistry has also increased greatly in recent years. As a result, many researchers now have the capability to examine the roles of specific pathways in pulmonary diseases through studies of lung tissues at the cellular and molecular levels.

Human lung tissues are widely available for study from excisions of lung lobes for possible cancer, lung volume reduction surgeries, lung transplantations, and video-assisted thoracic surgical lung biopsies. However, considerable expertise, expense, and effort are required for recruitment and clinical characterization of lung tissue donor subjects, lung tissue collection, and specimen processing. Processing of lung tissues for research is especially demanding since insufflation is required to preserve tissue architecture. These constraints limit the ability of many researchers, particularly basic scientists, to perform molecular histopathological research related to pulmonary diseases. The LTRC will enable mechanistic studies of disease using lung tissues by performing the prerequisite functions of donor subject recruitment and characterization and tissue collection and processing.

c. Description of Technical Requirements

The LTRC, through the Tissue Processing and Distribution Center, will facilitate histopathological research of pulmonary diseases by preparing and distributing to researchers collections of tissue specimens obtained at surgery. Collections of specimens will be linked to extensive clinical data appropriate to the specific disease. In general, donor subjects will be recruited for specific enrollment groups that are designed to address important research questions. Through this program the NHLBI expects to provide an important resource to the lung research community that will enhance elucidation of disease mechanisms and lead to better methods of preventing and managing various chronic lung diseases.

The LTRC will be comprised of up to 5 Clinical Centers (CCs), RFP–NHLBI–HR–04–08; a Tissue Processing and Distribution Center (TC), RFP–NHLBI–HR–04–09; the Radiology Center (RC), RFP–NHLBI–HR–04–10; and a Data Coordinating Center (DCC), RFP–NHLBI–HR–04–11. Offerors are strongly encouraged to read the RFPs for all of these components of the LTRC to better understand the overall structure and function of the consortium. A Steering Committee, consisting of the NHLBI Project Officer (non-voting member) and the Principal Investigator from each center awarded a contract under the above RFPs, will meet during Phase I to develop the LTRC Protocol Manual. Upon completion, the LTRC Protocol Manual will be submitted for review to an independent Scientific Advisory Committee (SAC), appointed by the NHLBI. The SAC will review the LTRC Protocol Manual and provide comments and advice to the NHLBI. During Phase II, the SAC will evaluate requests for access to LTRC resources and of research studies proposed by the CCs. An Observational Study Monitoring Board (OSMB) will be appointed by the NHLBI to monitor the protection of human research subjects and the overall progress and performance of the LTRC.

It is recognized that tissues from donor subjects with lung diseases other than COPD and idiopathic pulmonary fibrosis, especially rare conditions, would also be valuable to the lung research community. To allow for the collection and distribution of such lung tissues through the LTRC, the NHLBI intends to support collection of additional tissue specimens through a number of External Tissue Contributors (ETCs). These contributing sites will not carry out the extensive clinical characterization of donor subjects done by contracted Clinical Centers, but will provide tissue samples and clinical data extracted from the donor subjects' medical records. Proposals for ETCs will not be accepted in response to this solicitation. Centers interested in participating as an ETC are encouraged to contact the Data Coordinating Center after 8/1/2004 to obtain additional information. An ETC will be reimbursed for samples by the Data Coordinating Center using a capitated reimbursement mechanism. ETC investigators will not be represented on the LTRC Steering Committee nor will they receive funding for research studies through the LTRC.

d. Phasing

Phase I (6 months): The Principal Investigator from each of the awarded Clinical Centers, the Tissue Processing and Distribution Center, the Radiology Center, and the Data Coordinating Center will meet several times to identify enrollment groups and develop the LTRC Protocol Manual.

Phase II (54 months): The RC will train Clinical Center staff in procedures related to CT imaging. The RC will receive, analyze, and store CT images. A board-certified radiologist will perform a diagnostic evaluation of each CT image.

e. Clinical Research/Human Subjects

Research involving the transmission and analysis of CT image data from humans will be proposed in response to this solicitation. The following guidelines and policies, which may be applicable to this solicitation, can be viewed at: http://www.nhlbi.nih.gov/funding/policies

- Establishing Data and Safety Monitoring Boards and Observational Study Monitoring Boards
- Guidelines for Data Quality Assurance in Clinical Trials and Observational Studies
- Responsibilities of OSMBs Appointed by the NHLBI
- NHLBI Guidelines for Implementation of the Policy on Inclusion of Minorities and Women in Study Populations
- NHLBI Guidelines for Implementation of the Policy on Inclusion of Children in Research Involving Human Subjects
- Terms and Conditions for Accrual of Research Subjects in Research Supported by NHLBI
- Reporting Clinical Study Serious Adverse Events
- Medicare Coverage of Clinical Trials
- Human Tissue Repositories—Guidelines
- Tissue Sharing in Informed Consent—Guidance

f. Special Requirements

1. OMB CLEARANCE

After the LTRC Protocol Manual has been approved, a request for clinical exemption for LTRC-generated forms will be coordinated by the NHLBI Project Officer for submission to the NIH OMB Clearance Officer. It is expected that forms used by the LTRC to collect clinical data will be exempt from OMB clearance requirements.

2. CAPITATION REIMBURSEMENT

A capitation reimbursement system will be discussed and developed during Phase I for the participating Radiology Center. Capitation rates will be based on cost elements identified for performance of protocol procedures. Reimbursement of capitated costs will only be made after the Data Coordinating Center has verified to the Contracting Officer that the CT image data and analysis are complete and satisfy quality control standards specified in the LTRC Protocol Manual.

3. IRB Approval

The contractor will be required to obtain Institutional Review Board (IRB) approval of LTRC protocols related to activities of the Radiology Center.

g. Estimate of Effort

The Government considers the types of personnel and estimated levels of effort identified below to be required for successful completion of Radiology Center objectives. Effort is shown as a percentage of FTE (full-time equivalent) labor. The personnel and levels of effort listed below are for information only and are not to be considered restrictive for proposal purposes. The levels were formulated by NHLBI staff experienced in the conduct of multi-center clinical trials, utilizing recent experience.

Labor Category	Phase I	Phase II Core	Phase II Protocol Costs
Principal Investigator	30%	25%	10%
Radiologist	5%	5%	30%
Programmer	50%	11%*	0%
Image Analysis Technician	25%	25%	75%
Admin. Asst./Data Entry	25%	25%	25%
Total:	**135%**	**91%**	**140%**

* 50% in second half of Year 1; 25% in Year 2; 0% in Years 3-5

During Phase I a representative from each Center will meet in Bethesda, Maryland to develop the LTRC Protocol Manual. The Radiology Center (RC) will have primary responsibility for recommending procedures for CT image collection, electronic transmission, and analysis. During Phase II the RC will train Clinical Center staff in procedures related to CT imaging. The RC will receive, analyze, and store CT images. A board-certified radiologist will perform a diagnostic evaluation of each CT image. Core Costs will provide baseline support for RC infrastructure and staff. Protocol Costs will be reimbursed using a capitated system based on the number of CT images processed.

***Note**: Offerors shall ensure that the Principal Investigator and all other personnel proposed will not be committed on Federal grants and contracts for more than a total of 100% of their time. If the situation arises where it is determined that a proposed individual is committed for more than 100% of his or her time, the Government will require action on the part of the offeror to adjust the time commitment.*

h. Travel

Travel costs should be based on Steering Committee meetings in Bethesda, Maryland and one site visit to each Clinical Center.

During Phase I (6 months): Each center should propose travel costs based on two investigators attending four 2-day Steering Committee meetings in Bethesda, MD.

Phase II (54 months): Two investigators will attend two 2-day Steering Committee meetings in Bethesda, MD each year. Up to two individuals from the Radiology Center will site visit each Clinical Center during the first year.

i. Consortium Committees

The **Steering Committee**, consisting of the NHLBI Project Officer and the Principal Investigator from each participating center, will work together during Phase I to: 1) define enrollment groups of donor subjects useful for testing hypotheses regarding the etiology and/or pathogenesis of COPD or idiopathic pulmonary fibrosis; 2) establish inclusion/exclusion criteria for enrollment groups based on characteristics that can be determined prior to surgery and without clinical testing; 3) determine a target number of donor subjects to be recruited in each enrollment group; 4) finalize the LTRC Protocol Manual, and 5) provide scientific direction to the LTRC at an operational level. During Phase I, the Steering Committee will meet approximately monthly, including four meetings and teleconferences as needed. During Phase II the Steering Committee will meet twice a year and conduct teleconferences as needed. Each participating center will have one vote on issues pertaining to the LTRC.

A **Scientific Advisory Committee** (SAC), appointed by the NHLBI, will make recommendations to the NHLBI regarding the consortium protocols. The SAC will review the LTRC Protocol Manual and amendments thereto regarding feasibility and potential for accomplishing LTRC objectives. The SAC will also evaluate research proposals involving LTRC specimens and clinical data. The SAC will meet twice during Phase 1 and once per year thereafter and will conduct teleconferences as needed.

An **Observational and Study Monitoring Board** (OSMB) will be established to monitor progress, data outcomes, and patient safety. The Board will periodically evaluate consortium procedures, review results for adverse events, and advise the NHLBI when changes should be made. The Board will meet once per year and conduct teleconferences as needed. Responsibilities of OSMBs appointed by the NHLBI can be found at: http://www.nhlbi.nih.gov/funding/policies/osmb_inst.htm

j. Past Performance

Offerors shall submit the following information as part of their business proposal (for both the offeror and proposed major subcontractors): A list of the contracts, grants, or cooperative agreements completed during the past two (2) years and all contracts currently in progress for products or services similar to the solicitation workscope. The list may include agreements entered into with the Federal Government, agencies of state and local governments, and commercial organizations. Offerors that are newly formed entities without prior contracts should list contracts and subcontracts performed by all proposed key personnel. Include the following information for each contract or subcontract:

1. Name of Contracting Organization
2. Contract Number (for subcontracts, provide the prime contract number and subcontract number)
3. Contract Type
4. Total Contract Value
5. Description of Requirement
6. Contracting Officer's Name, Telephone Number, and E-mail Address
7. Project Officer's Name, Telephone Number, and E-mail Address

Each offeror will be evaluated on its performance under existing and prior contracts for similar products or services. Performance information will be used for responsibility determinations. The Government will focus on information that demonstrates quality of performance relative to the size and complexity of the acquisition under consideration. The Government is not required to contact all references provided by the offeror. References other than those identified by the offeror may be contacted by the Government to obtain additional information that will be used in the evaluation of an offeror's past performance.

k. Offerors Must Address

In order to expedite the finalization of the LTRC Protocol Manual within the Phase I time line, offerors shall:

1. Document the capabilities of the Principal Investigator with regard to participation on the Steering Committee, including leadership abilities and expertise in lung imaging.
2. Document experience in providing radiological support services to multi-center clinical studies of lung diseases.
3. Describe proposed procedures and methods for chest CT image acquisition in the Clinical Centers, including consideration of different hardware systems that may be utilized, and for electronic transmission of images to the RC.
4. Propose in detail procedures and methods for image reconstruction, transmission to the RC, and visualization for diagnostic evaluation.
5. Propose procedures for quality assurance and quality control of the CT images transmitted to the RC by the Clinical Centers and for the analysis by the RC of the images.
6. Provide a detailed description of proposed procedures for obtaining measures of lung disease from CT images.
7. Describe proposed plans for training Clinical Center personnel in methods of chest CT image acquisition and transmission.
8. Describe plans for assuring the protection and privacy of human research subjects. Provide

documentation of an Office of Human Research Protections–approved assurance (e.g., a Federal Wide Assurance).

9. Describe the computer systems and software that will be employed by the RC to perform image analysis, storage, and backup. Describe the computer systems and software that will be required at the Clinical Centers to transmit images.

10. Describe the administrative structure of the proposed RC.

11. Describe any institutional commitments that will be provided if selected for award.

12. Provide a detailed description of facilities that will be used to carry out the Statement of Work. This should include resources necessary to handle the receipt and storage of CT images. For proposal purposes offerors should assume 810-1620 images will be received at the Radiology Center. The expected number of images will be determined during Phase I.

    Note: *Offerors from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. In such a case, a letter of agreement from the GCRC Program Director and the Principal Investigator shall be included with the technical proposal. Clear distinction should be made in the proposal between tasks and facilities funded by the GCRC and those requiring reimbursement under this contract*

13. Provide any other information needed to allow reviewers to judge the capability of the offeror to accomplish the Statement of Work of the RC.

ARTICLE C.1. STATEMENT OF WORK

Independently and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government as needed to perform the Statement of Work below. The Contractor shall deliver the items specified in ARTICLE C.2. to the destination indicated in ARTICLE F.1.

The Radiology Center (RC) shall develop protocols related to chest computed tomographic (CT) image acquisition, processing, and transmission; perform diagnostic analyses of CT images collected for the LTRC; maintain an archive of CT images; and extract quantitative indices of disease severity from the lung images. The RC shall perform the following tasks:

Phase I (01/30/2004 to 07/31/2004, 6 Months)

1. Provide one member of the Steering Committee with expertise in lung imaging who will participate fully in the activities of the Steering Committee. The Steering Committee will develop the Lung Tissue Research Consortium Protocol Manual that establishes:

    a. Groups of donor subjects to be enrolled (selected for testing hypotheses regarding the etiology and/or pathogenesis of COPD or idiopathic pulmonary fibrosis). Inclusion/exclusion criteria for enrollment groups based on characteristics that can be determined prior to surgery and without clinical testing. Target numbers of donor subjects to be recruited in each enrollment group. Tissues to be collected (e.g., lung parenchyma, blood), clinical testing to be performed (e.g., pulmonary function testing, chest computed tomography (CT)), and data to be collected or extracted from the donor subjects' medical records (e.g., medical diagnoses, previous spirometry, pathology reports, questionnaires) for each enrollment group.

    b. Protocols for chest CT imaging and for specimen processing and transport. Protocols and forms for donor subject screening, for clinical characterization, and for data entry and transmission.

Protocols for clinical data, CT image, and biological specimen quality control/quality assurance/quality rating.

2. Develop procedures and standards for performance of chest CT examinations, acquisition of images, and electronic transmission of images to the RC. Finalize LTRC Protocol Manual chapter(s) detailing methods, including security measures to ensure the confidentiality and privacy of research subjects.

3. Develop standards and procedures for assessing the technical quality of CT images transmitted to the RC. Finalize LTRC Protocol Manual chapter(s) detailing quality assurance and quality control procedures for the Clinical Centers and the RC, related to CT imaging.

4. Develop procedures for obtaining quantitative and/or semi-quantitative measures of lung disease (e.g., percent emphysema by radiographic density) from CT images. Where possible, measures specific to the resected portion of lung should be obtained. Prepare LTRC Protocol Manual chapter(s) detailing methods for obtaining these measures.

5. Develop computer systems and software needed for electronic transmission of CT images from the Clinical Centers to the RC.

6. Develop plans, materials, and LTRC Protocol Manual chapter(s) for training and certifying personnel involved in performing radiographic studies and transmitting CT images.

7. Work with the Data Coordinating Center to submit the LTRC Protocol Manual, and any amendments thereto, to the Scientific Advisory Committee (SAC) for review and comment. The Protocol Manual shall be finalized and submitted to the SAC no later than June 30, 2004. The SAC members, appointed by the NHLBI, will make recommendations to the NHLBI regarding the final consortium protocols. The contractor shall not begin work on Phase II activities until written approval has been received from the Contracting Officer.

8. Obtain Institutional Review Board (IRB) approval for activities of the RC described in the LTRC Protocol Manual and any amendments thereto.

Phase II (08/01/2004 to 01/29/2009, 4 years 6 months)

In accordance with the LTRC Protocol Manual the contractor shall:

1. Within the first two months of Phase II, train and certify Clinical Center personnel involved in CT imaging and transmission of images to the RC.

   ***Note**: Training may employ written materials, web-based instruction, videotaped presentations, and telephone or video conferencing.*

2. Conduct a site visit to each Clinical Center, within the first six months of Phase II, to ensure compliance with LTRC protocols and standards.

3. Assist Clinical Center personnel in transmitting CT image data to the RC. Store CT images in a secure manner and in a format that is accessible without the use of proprietary software.

4. Assess and report the technical quality of each CT image transmitted to the RC using standards and procedures specified in the LTRC Protocol Manual. Suggest to the Steering Committee any needed modifications in the methods of image acquisition and transmission.

5. Establish and maintain a system for tracking the receipt and analysis CT images. Prepare monthly Image Summary Reports.

6. Perform a diagnostic analysis of each CT image. This analysis will be performed by a board-certified radiologist. Transmit a written report of any abnormalities found to the Data Coordinating Center and

to the Clinical Center from which the image originated for relay to the donor subject's primary care physician in accordance with the LTRC Protocol Manual.

7. Analyze each CT image to obtain quantitative and/or semi-quantitative measures of lung disease according to procedures specified in the LTRC Protocol Manual.

8. Transmit anonymized CT images in electronic form to researchers as directed by the Data Coordinating Center and in accordance with the LTRC Protocol Manual.

9. The Principal Investigator shall participate fully in the activities of the Steering Committee to:

    a. Identify lung conditions other than COPD and idiopathic pulmonary fibrosis for which lung tissues are needed for research and may be available from External Tissue Contributors (ETCs). Define inclusion/exclusion criteria for auxiliary groups of donor subjects appropriate for research of these conditions, set target numbers of donor subjects for each group, determine what tissues are to be accepted (e.g., surgical specimens, transbronchial biopsies), and determine what data should be extracted from the donor subjects' medical records in each of these groups.

    b. Identify any problems with existing LTRC procedures and any difficulties that may interfere with LTRC objectives. Devise strategies to improve procedures and overcome difficulties. Submit recommended changes in policies and protocols to the Scientific Advisory Committee for evaluation.

10. Work with other LTRC investigators to prepare reports and manuscripts for publication.

11. Provide CT images as a data set with full documentation. The documentation shall be clear to allow for use by investigators not familiar with the data set.

ARTICLE C.2. REPORTING REQUIREMENTS

Technical Progress Reports

In addition to those reports required by the other terms of this contract, the Contractor shall prepare and submit the following reports in the manner stated below and in accordance with ARTICLE F.1. DELIVERIES of this contract.

a. Image Analysis Report: During Phase II, for each CT image, transmit in electronic form a tabulation of quantitative and/or semi-quantitative measures of lung disease obtained according to the LTRC Protocol Manual.

b. Monthly Image Summary Report: Throughout Phase II, submit a Monthly Image Summary report to the Data Coordinating Center. The report shall include: 1) a list of the images received during the month and cumulative totals by Clinical Center; 2) a rating of the technical quality of each CT image according to LTRC Protocol Manual. The first reporting period consists of the first full calendar month of performance plus any fractional part of the initial month. Thereafter, the reporting period shall consist of one calendar month.

c. Abnormality Report: Throughout Phase II, submit Abnormality Reports to the Data Coordinating Center and the Clinical Center from which the CT image originated. This report of diagnostic analysis of the CT image by a board-certified radiologist shall be submitted within one week of receipt of the CT image at the RC.

d. Semi-Annual Progress Report: A comprehensive Semi-annual Progress Report reflecting all activities conducted during the performance period. The report, in a narrative form, shall be concise and informational. Extensive reference material is not desired, but such references as are necessary to full understanding may be included. The report shall be written in sufficient detail to allow use as a

reference document. The Semi-annual Progress Reports shall include but not be limited to:

i. A cover page containing the following information:
    1. Contract number
    2. Contractor's name and address
    3. Principal investigator
ii. Description of overall progress.
iii. Current problems which may impede performance and proposed corrective actions.
iv. The numbers of images received and analyzed.
v. Scientific progress made, including a list of manuscripts published or accepted for publication related to LTRC objectives.
vi. Work to be performed during the next 6 months.

A Semi-Annual Progress Report will not be required for the period when the Final Report is due.

d. Abstracts and manuscripts published or accepted for publication shall be provided in accordance with the LTRC Protocol Manual.

e. Final Report: The report is to include a summation of the work performed and results achieved for the entire contract period of performance. The report shall be in sufficient detail to describe comprehensively the results achieved.

f. CT Image Data Sets: During Phase II, prepare CT image data sets for distribution to investigators in accordance with the LTRC Protocol Manual. Data sets shall be prepared in accordance with the NHLBI Limited Access Data Clause (See: http://www.nhlbi.nih.gov/resources/deca/policy.htm).

g. Complete CT Image Data Set: The final data set shall include all CT image data with full documentation. The documentation shall allow for use by investigators not familiar with the data set. The documentation shall be written in Word Perfect, Word, or ASCII format, and shall be prepared in accordance with the NHLBI Limited Access Data Clause (See: http://www.nhlbi.nih.gov/resources/deca/policy.htm